INFECTION AND CHILDHOOD LEUKEMIA

Current hypotheses under study and gene-environment interactions

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A SPECIFIC INFECTION MAY BE RESPONSIBLE FOR A SUBSET OF CHILDHOOD LEUKEMIA

- **Animal models**
  - *Herpes virus* Marek (chicken)
  - *Retrovirus* Bovine, feline, avian, murine leukemia
- **Human hematopoietic malignancies**
  - *Herpes virus* EBV in Burkitt and Hodgkin lymphoma
  - *Retrovirus* HTLV1 in ATL
  - *Bacteria* Helicobacter pylori ingastric lymphoma

A SPECIFIC INFECTION MAY BE RESPONSIBLE FOR A SUBSET OF CHILDHOOD LEUKEMIA – no direct evidence

- **Serology**
  EBV
  HZV
- **Viral genomes sequencing**
  Herpes (EBV, HHV 4,5,6,7,8)
  Polyomavirus (JC, NK)
  Parvovirus (B19)
  Adenovirus
  Animal leukemia virus
  TT

Unrecognized sequences?
Elimination of viral sequences after prenatal/early infection?
…

Adenovirus DNA increased in Guthrie cards of ALL *(Gustafsson et al, 2007)*

Maternal reactivation of EBV and childhood leukemia *(Tedeschi et al, 2007)*

A SPECIFIC INFECTION MAY BE RESPONSIBLE FOR A SUBSET OF CHILDHOOD LEUKEMIA – indirect evidences

Clustering

If leukemia were caused by an infectious agent, then cases should occur closer in space and time than predicted by Poisson distribution

- Overdispersion (Potthoff-Whittinghill)
- Spatial heterogeneity (Tango, Rogerson)
- Space time interaction (Knox, Diggle)
- Spatial/space-time clusters (Kulldorff)

Weak evidence of slight overdispersion

- Assumes spatial heterogeneity … overdispersion homogeneous all over the territory
- Most geographical units are poorly informative (O ≤ 1)

Some weak evidence of space-time interaction in cases 0-4 years old

- Arbitrary distances in time and space
- Inadequate if population shifts over the time period not uniform

Inserm
Institut national de la santé et de la recherche médicale

A SPECIFIC INFECTION MAY BE RESPONSIBLE FOR A SUBSET OF CHILDHOOD LEUKEMIA

Population mixing and Kinlen's hypothesis *(Kinlen, 1988)*

Clustering

incidence ↗ with population mixing?

(Kinlen, 1988)

Leukemia is a rare consequence of an infection by one or several common and specific agents. Micro-epidemics can occur when population mixing create conditions for contacts between infective and non-immune susceptible people.

- Unusual, extreme, population mixing *(Kinlen, 2004)*
- More usual population movements
- Time of birth? Time of diagnosis?

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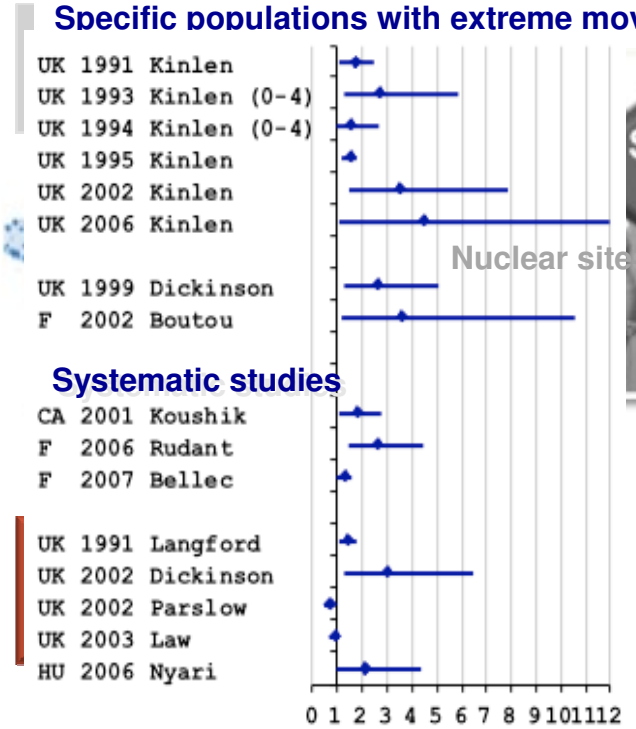

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In utero/prenatal infection *(Smith et al, 1997)*

(Smith et al, 1997)

ALL could result from an *in utero* exposure to a specific infection, with a latency period of 2 years on average

Improvement of hygiene would increase the probability that infection occur

- *In utero* (increased number of susceptible mothers)
- in early childhood (increased number of children unprotected by maternal antibodies)

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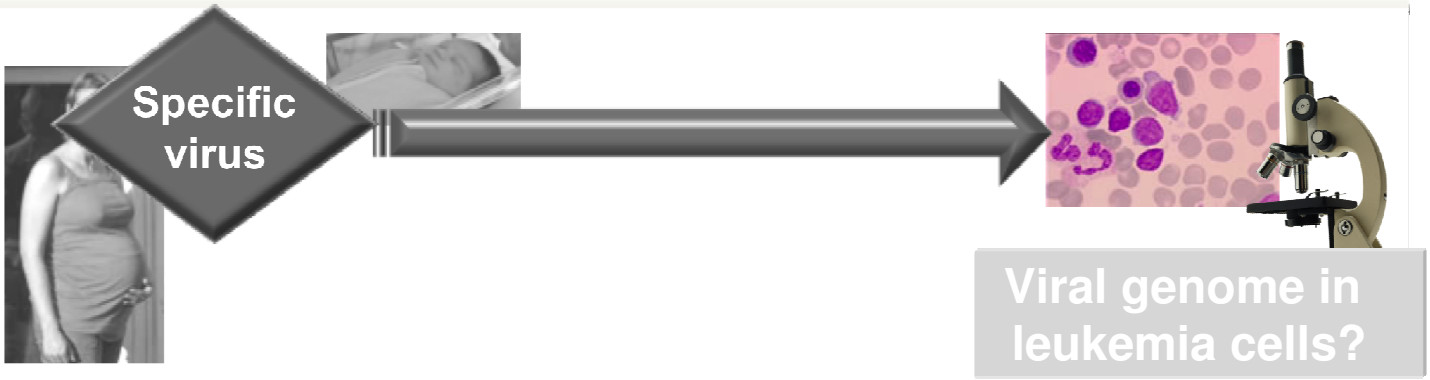
Clustering



incidence ↗ with population mixing?

Genetic and epigenetic factors can modulate

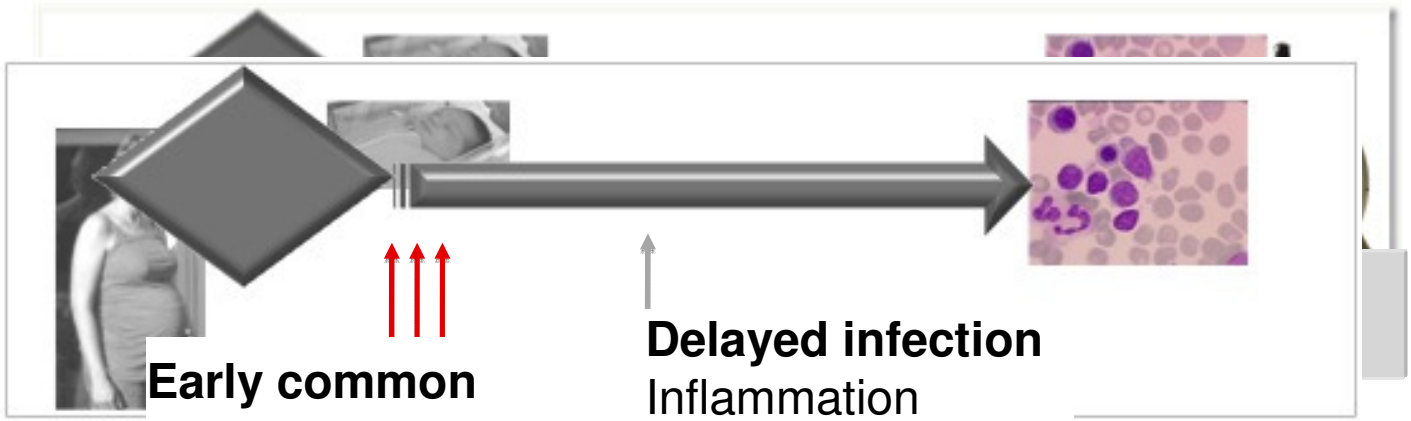
- **Probability of contracting an infection**
- **Efficiency of the response to infections**
- **Probability of triggering a genetic event**
- **…**

(see later)

COMMON INFECTIONS IN CHILDHOOD INFLUENCE THE RISK OF CHILDHOOD LEUKEMIA

Clustering

incidence ↗ with population mixing?



Early common infections

Day care

Birth order…

Breast-feeding

Delayed infection
Inflammation
Oxidative stress
….

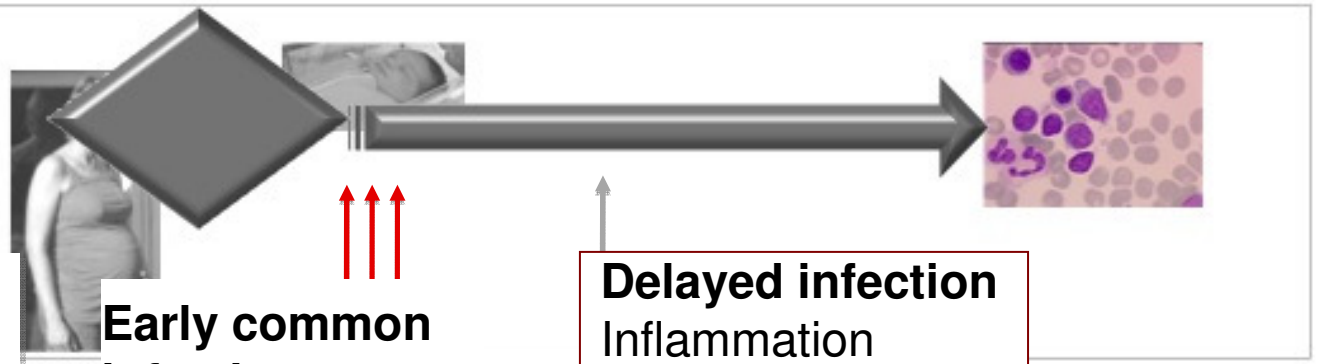
Stimulation of immune response

HYGIENE, DELAYED INFECTIONS AND GREAVES' HYPOTHESIS *(Greaves, 1988)*

Prenatal events

t(12;21) TEL-AML1
Hyperdiploidy
(Greaves & Wiemels,2003)

t(8;21) AML1–ETO
PML-RARα
MLL



Early common infections

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….

(Greaves, 1988)

Many ALL (c ALL) arise as a consequence of an abnormal response to common delayed infection in a two-stage process

- The first oncogenic event occurs during fetal hematopoiesis, resulting in a clone of preleukemic cells (direct evidence)
- A second and post-natal oncogenic event may occur in the course of an unadapted response to common infections

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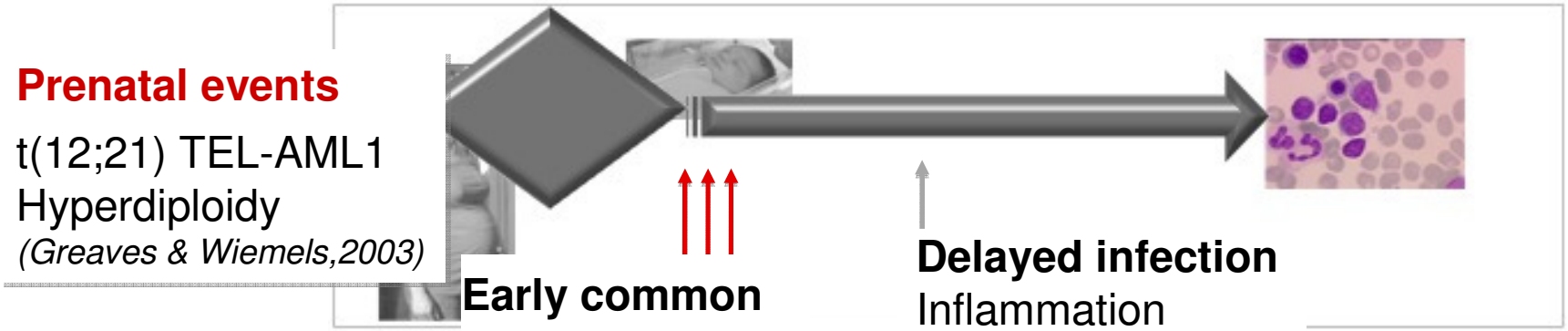

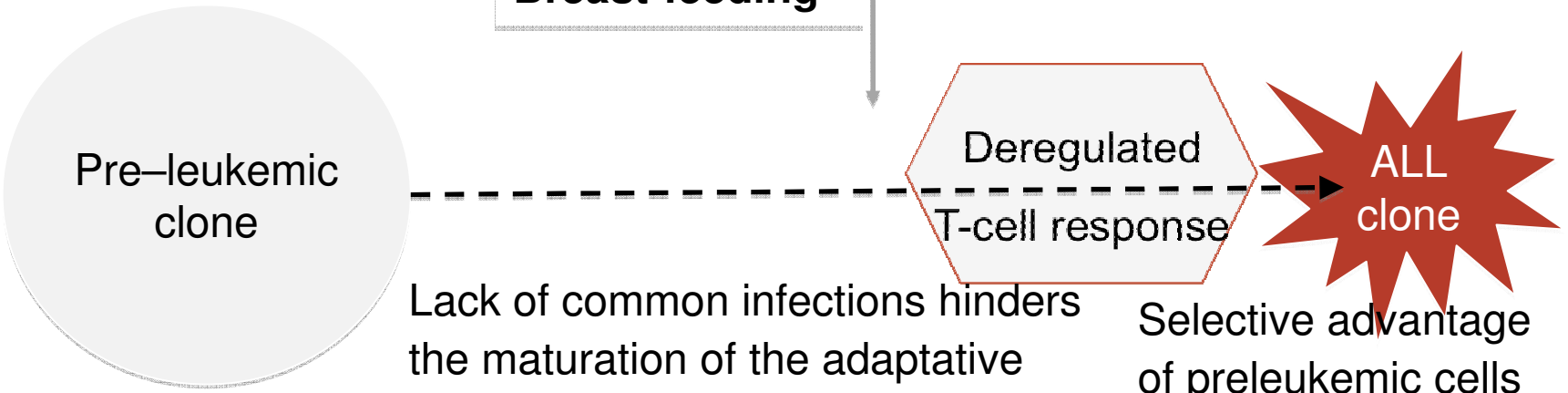

Lack of common infections hinders the maturation of the adaptative immune system

Selective advantage of preleukemic cells (≈ 1% of carriers)

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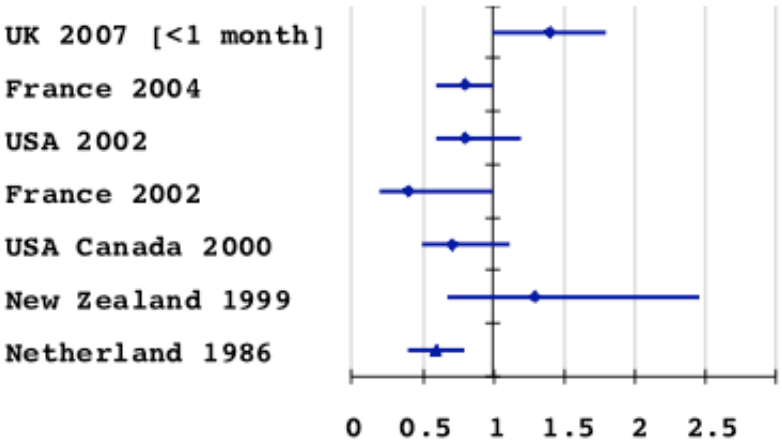
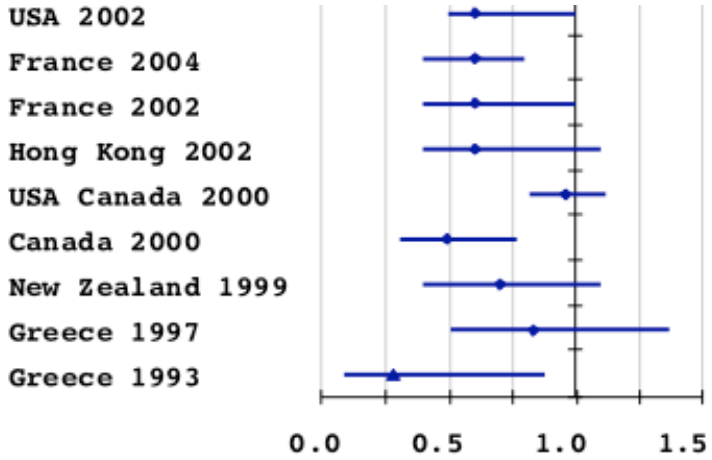


Birth order

Day-care



Breast feeding

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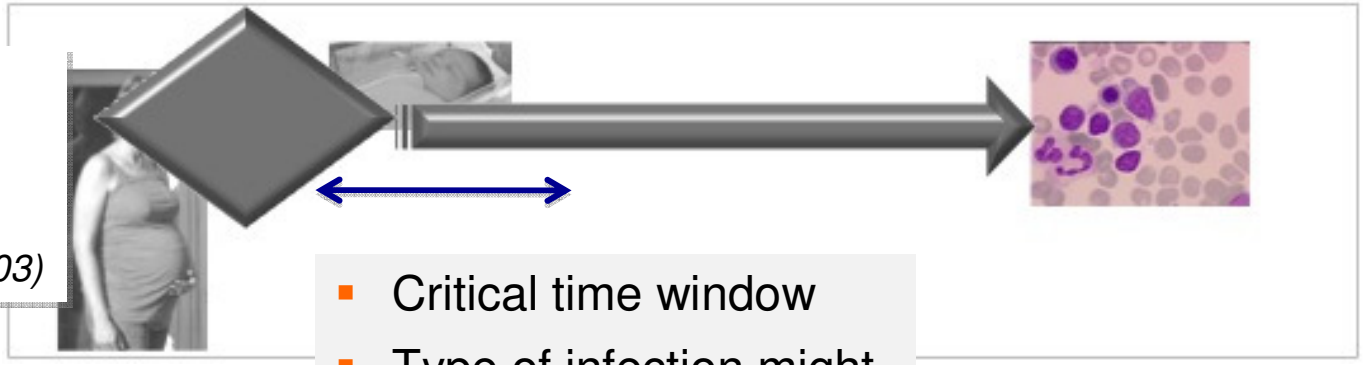
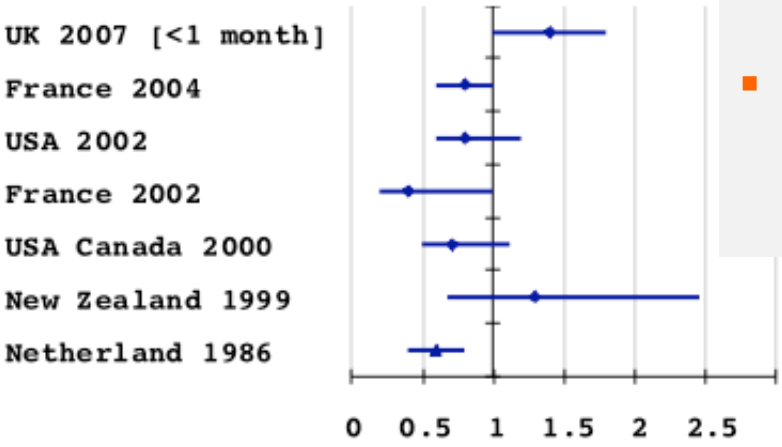


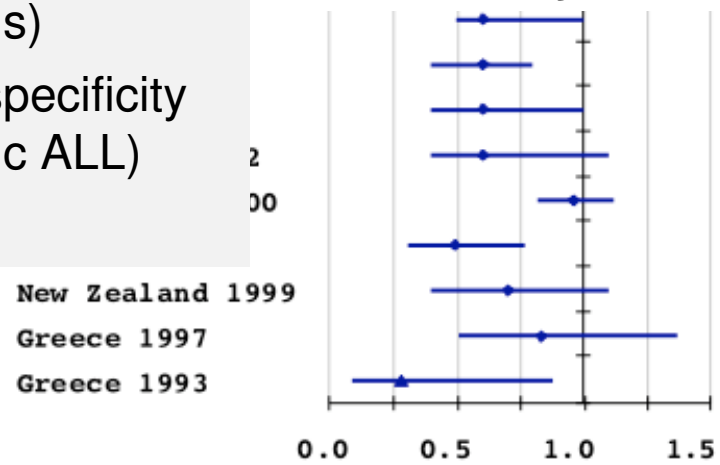
- Critical time window
- Type of infection might be relevant (URTI, gastroenteritis)
- No obvious specificity for ALL (and c ALL)

Early common infections



Birth order

Day-care



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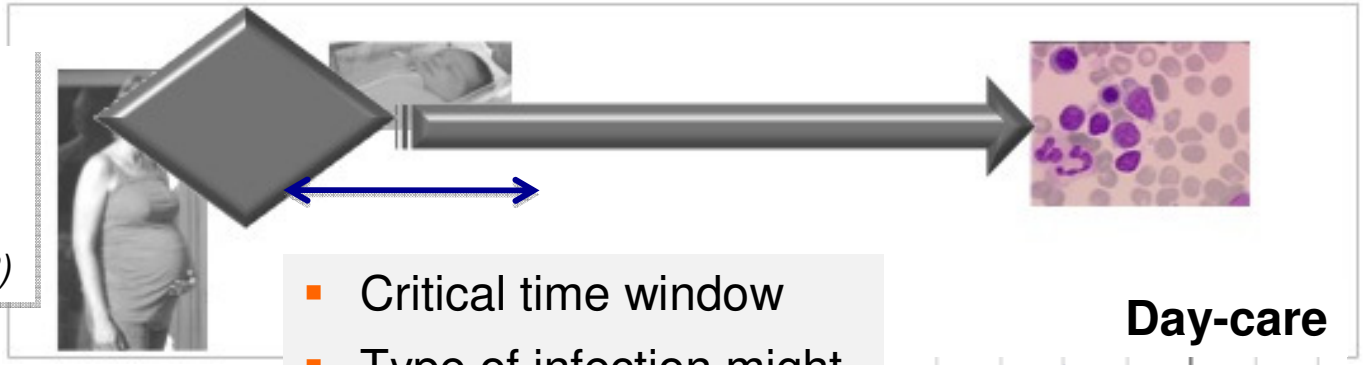

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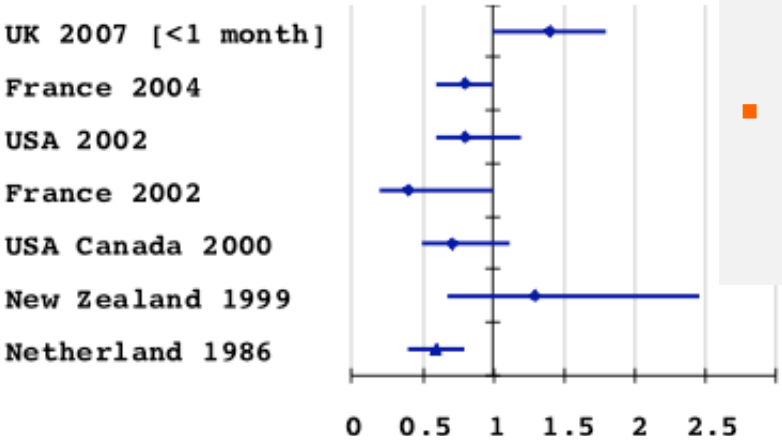

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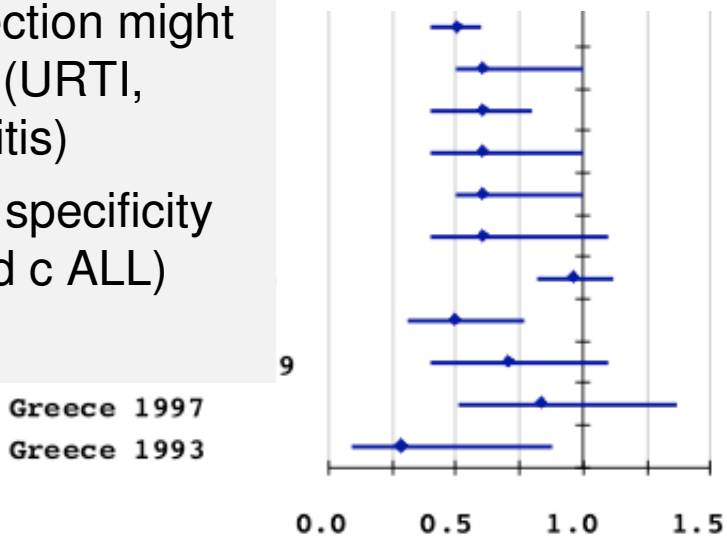
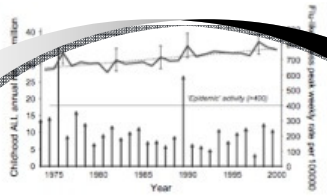


- Diagnosed infections *vs* infection carriage
- Reliability of interview? (*Roman et al, 2007)*

- Different meaning between countries?
- Strongly related to birth order (sensitive to control selection)

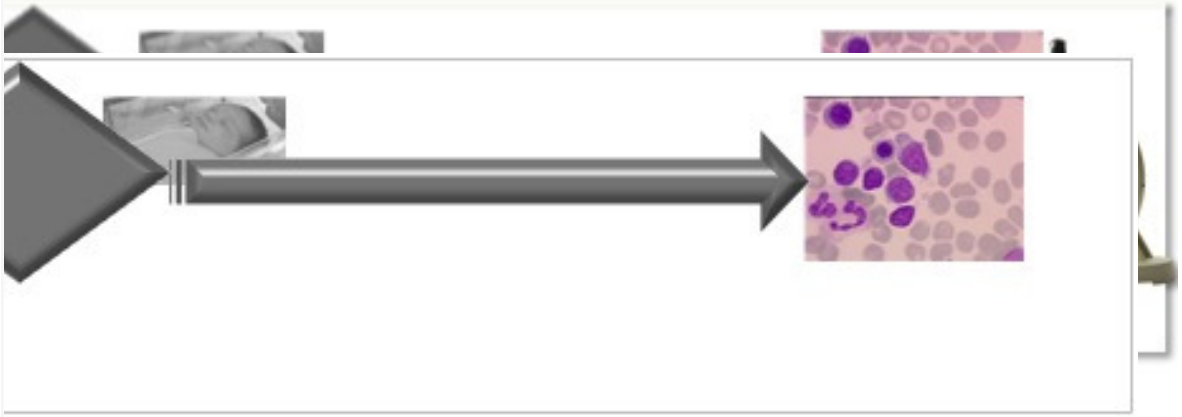
Link with infectious diseases



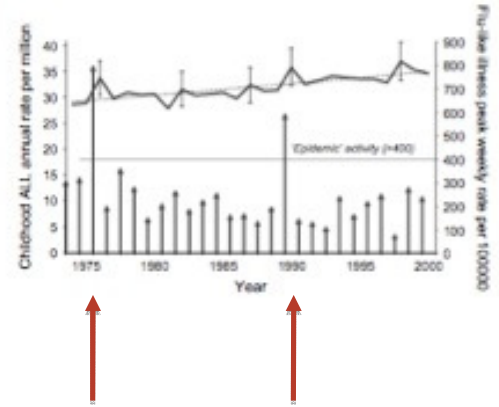
Adenovirus **Measles** **Rotavirus** **EBV** **Chicken pox** **CMV** **Roseola** **Mumps** **Influenza**

- **Childhood infections**
- **Maternal infections during pregnancy**
  Influenza

?



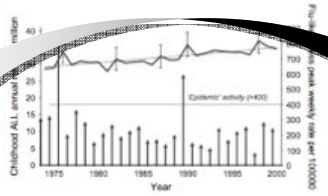
- **Ecological link** influenza x c-ALL *(Kroll et al, 2006)*



Correlation between infection x leukemia incidences

- One of these common viruses might be directly responsible for leukemia
- They may alter immune defense against leukemia virus
- They may result from conditions that also promote leukemia virus
- They may trigger leukemic transformation of preleukemic clones

Link with infectious diseases



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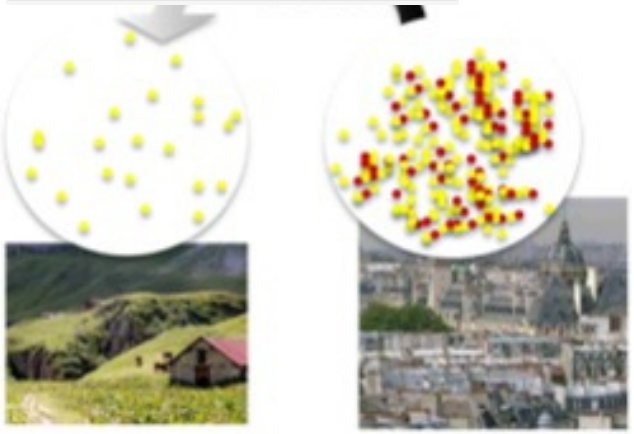
Delayed infections

incidence ↗ with population mixing?



Genetic and epigenetic factors can modulate

- **Probability of contracting an infection**
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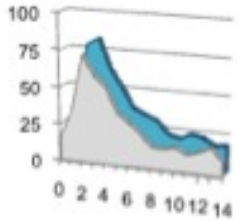
- **…**

GENETIC/EPIGENETIC PREDISPOSITION

Very few data on childhood leukemia

- **Variability of adaptative immune response and childhood leukemia**
  - HLA class II (T-cell response to many viruses including herpes virus)
    - HLA DRB4 and ALL *(Dorak et al, 1999)*
    - HLA-DPB1 and c ALL *(Taylor et al, 2008)*
- **Male gender**
  - HLA DRB4 and ALL *(Dorak et al, 1999)*
  - HLA-DQA1/B1 and c ALL *(Taylor et al,1998)*



GENETIC PREDISPOSITION

Gene x infection interactions in other lymphoid malignancies

- **Susceptibility to virus transmission**

  HTLV1 (Adult T cell Leukemia)
  (segregation analysis: dominant control of infection transmission through breast-feeding - *Plancoulaine et al, 2006*)

  EBV (some Hodgkin and Burkitt lymphomas)
  (segregation analysis of anti-VCA IgG titers - *Besson et al, 2007*)

- **Rare inherited immune deficiencies**

  Various primary immune deficiencies and EBV-related lymphoma

  XLP and EBV (lymphoma) *(Purtilo, 1981)*

- **Polymorphisms in genes of the immune response**

  TNFα and IL10 in non-Hodgkin lymphoma *(Rothman et al, 2006; Purdue et al, 2007)*

GENETIC/EPIGENETIC PREDISPOSITION

Other candidate polymorphisms in lymphoid response to infection

- **Immune response and inflammation**
  - T-cell response pathway
  - Negative relationship with asthma but shared association with delayed infection
  - Relationship with TNF and Th2 pathway? With innate immunity pathways?
- **Cell homeostasis**
  - Cell cycle control, DNA repair, apopotosis…
- **Metabolism of xenobiotics – response to oxidative stress**
- **Epigenetic modulation**

In conclusion

Many indirect evidences for an infectious origin of childhood acute leukemia

Critical period of the very early life still needs better characterization

Many pathways subject to interindividual variability are expected to modulate the risk

No epidemiological data to date on epigenetic modulation of risk.

Further understanding of infection x genetic interactions

- Exploiting large and well designed studies
  - Case-control studies and consortium with good information on early infections and related variables (CLIC)
  - Cohort consortium with prospective data describing infections during the first months (I4C)
- Collecting/exploiting data from informative sub-populations
  - Familial data (susceptibility to infection)?
  - Some case clusters (infection)?
- High-throughput reliable platforms and appropriate statistical methods
- Multidisciplinary partnerships required